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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,045	11/13/2001	Timothy R. Brazelton	286002021300	8147

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,045	BRAZELTON ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *22-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3/12/02* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I in Paper No. 7 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement for grouping the invention, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicants do indicated however the species as indicated in Paper #6 are not patentably distinct with respect to different types of neuron deficiencies, and neuronal growth factors. The argument is not persuasive because applicants fail to submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. Moreover, numerous *diseases* and *growth factors* are involved, each type of disease has its distinct etiology and pathogenesis, and each type of neuronal factor has its distinct biological characteristics and different mode of operation, the divergent subject matter would require different fields of search. Examination of all species would impose serious burden on the Office. However, as indicated in the Restriction requirement, upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a). The prosecution will also follow the following rule on record, "Should applicant traverse on the ground that the species

are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention". M.P.E.P. states, "FOR PURPOSES OF THE INITIAL REQUIREMENT, A SERIOUS BURDEN ON THE EXAMINER MAY BE PRIMA FACIE SHOWN IF THE EXAMINER SHOWS BY APPROPRIATE EXPLANATION OF SEPARATE CLASSIFICATION, OR SEPARATE STATUS IN THE ART, OR A DIFFERENT FIELD OF SEARCH AS DEFINED IN MPEP § 808.02". Therefore, it is maintained that these inventions are distinct due to their divergent subject matter. Further search of these inventions is not co-extensive. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Please note that claims 6 & 7, and the species of neurodegenerative disorders have been rejoined with the elected invention as no severe search burden was imposed on the Office. Claims 1-34 are pending, however, claims 22-34 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to

non-elected inventions, there being no allowable generic or linking claim. Claims 1-21 are under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims are directed to treating neuronal deficiency, preferably congenital disorders due to teratogen or neurodegeneration, comprising administering bone marrow derived cells to an individual in need thereof by any route of administration, wherein at least one symptom of the disease is ameliorated.

The specification teaches that bone marrow-derived cells have been found to give rise to additional cell types in addition to hematopoietic cells, that such cells could be used to treat certain neuronal deficiencies. In the working examples, the specification teaches that three months after *intravenous* injection, bone marrow-derived cells were identified in the brain of injected mice, and some cells expressing neuronal cell surface markers and/or having neuronal cell morphology. However, the specification fails to teach whether the bone marrow-derived cells administered either locally or any site remote from the site of disorder generated sufficient amount of neuronal cells at the site of the lesion, and differentiated to the neuronal phenotype desired for treating a particular deficiency, such that at least one symptom of a congenital disorder such as fetal alcohol syndrome could be ameliorated, thus, fails to provide an enabling disclosure to support the full scope of the claims.

Fetal alcohol syndrome (FAS) is a congenital disorder caused from embryo alcohol teratogen exposure. FAS is characterized by retarded growth, various abnormalities of the central nervous system, and characteristic abnormalities of the face and head. So far, there is no report on record that such disorder could be treated by any medication or stem cell transplantation. It is common sense that treating such a disease caused by possibly numerous defects in different neuronal and other cell types require

sufficient quantity of new neurons, differentiated to a desired neuronal phenotype such as dopamine-producing cells, at a proper anatomical location, administered at certain stage of a disease, and sustained presence of these new neurons. However, neither the art of record nor the specification addresses these issues relevant for a clinical benefit treating neuronal deficiency. For example, *Burt et al* (Blood 1998;91:2609-16) teach in an experimental autoimmune encephalomyelitis model that transplantation of bone marrow-derived cells only slightly improved acute inflammatory infiltration, and failed to improve clinical disease when the treatment is performed in the chronic stage. They concluded that only in the absence of glial scarring and irreversible neuronal injury, the transplantation might be beneficial (e.g. abstract). In the FAS disease, wherein the permanent and irreversible neuronal damage has caused before the birth, thus, it is highly unpredictable whether the insignificant amount of new neurons derived from the transplantation of bone marrow-derived cells would reverse or ameliorate any symptom of FAS in light of the teaching of *Burt et al*. Therefore, specific but not general teaching is required for the skilled artisan intending to practice the claimed invention for ameliorating FAS and other congenital disorders. *Sugaya et al* (CMLS 2003;60:1891-1902) review at a post-filing date the state of the art for neuronal stem cell transplantation. *Sugaya et al* teach bone marrow derived cells as a source of neuronal stem cells, acknowledge the promising experimental progress in animal models, and point to practical issues remaining for neuron stem cells becoming a viable therapeutic tool. *Sugaya et al* teach, "BEFORE WE BEGIN TO DEVELOP CLINICAL APPLICATIONS, WE MUST CONSIDER ENVIRONMENTAL FACTORS THAT HAVE NOT BEEN DISCUSSED IN THE CURRENT

PRECLINICAL APPLICATIONS" (abstract), "RESEARCHERS HAVE SUCCEEDED IN RECOVERING BRAIN FUNCTION IN ADULT ANIMAL MODELS BY TRANSPLANTATION OF STEM CELLS...NONETHELESS, THESE STUDIES DID NOT TAKE INTO ACCOUNT THE EFFECT OF PATHOLOGICAL CHANGES THAT MAY OCCUR IN THE DISEASED BRAIN AND THAT MAY PREVENT THE NORMAL DIFFERETIATION OR MIGRATION OF STEM CELLS" (2nd paragraph, right column, page 1894), and concluded, "CLINICAL TRIALS OF STEM CELL TRANSPLANTATION FOR NEUROLOGICAL DISEASES MAY BE AN IMPORTANT EXPERIMENTAL APPROACH BUT MAY TAKE MORE STUDY OVER A LONGER TIME PERIOD FOR ALL TRANSPLANTATION TO BE ESTABLISHED AS A VIABLE THERAPY" (Conclusion, page 1899). *Galvin et al* (MJA 2002 ;177:316-8) review at a post-filing date the state of the art for neuronal stem cell transplantation. *Galvin et al* is optimistic that human neuronal stem cell biology is poised to make an impact on clinical neural transplantation programs, "HOWEVER, THERE IS GRAVE DANGER THAT THE RUSH TO APPLY STEM CELL THERAPIES IN ACTUAL PATIENTS MAY LEAD TO SCIENTIFICALLY ILL-FOUNDED CLINICAL TRIALS THAT LACK SUPPORT FROM RIGOROUS PRECLINICAL RESEARCH". The apparent insufficiencies are lack of primate model to allow potential risks and benefits to be adequately assessed, the lack of sophisticated control of desired neuronal phenotypes and obtaining clinically significant quantities of stem cells. They teach, "CLINICAL TRIALS SHOULD NOT BE INITIATED ON THE BASIS OF RESULTS FROM A LIMITED NUMBER OF RODENT STUDIES", and "TRIALS IN HUMAN PATIENTS SHOULD NOT BE INITIATED UNTIL: NEUROLOGICAL TESTING SHOWS SIGNIFICANT AND LONG-LASTING FUNCTIONAL RECOVERY AFTER TRANSPLANTATION EXPERIMENTS IN WELL-CHARACTERISED ANIMAL MODELS OF HUMAN CNS DISORDERS". In view of the foregoing teachings, the instant claims do not appear to be enabled in the absence of evidence to the contrary.

Moreover, the transplantation was performed in the isogeneic mouse and the claims encompass and preferably require treatment performed in human, which is significantly more difficult to achieve. *Donovan and Gearhart* (Nat 2001 Nov;414:92-97) teach "HUMAN STEM CELL POPULATIONS PROLIFERATE MORE SLOWLY THAN THEIR MURINE COUNTERPARTS, DIFFERENTIATE MORE READILY AND THEIR CLONING EFFICIENCY IS VERY LOW" (last paragraph on page 95), "ONLY TIME WILL TELL WHETHER THE RESULTS OF CELL TRANSPLANTATION IN ANIMAL MODELS CAN BE RECAPITULATED IN HUMANS AND WHETHER IT WILL PROVE IMPOSSIBLE TO MAKE CERTAIN CELL TYPES FROM PLURIPOTENT STEM CELLS" (last paragraph on page 96). *Weissman* (Science 2000;287:1442-46) teaches that although clinical stem cell transplantation could greatly add to the physician's armamentarium against degenerative diseases, there are still long way to go in reality. The barriers are the complicated immunological responses from the host to the transplanted cells, and the state of primary diseases of these patients (see the entire article). The take-home message is "IT IS REASONABLE TO EXPECT THAT COTRANSPLANTATION OF HSCS AND TISSUE OR ORGAN STEM AND PROGENITOR CELLS WILL OCCUR INCREASINGLY OVER THE NEXT TWO DECADES AND WILL RESULT FROM THE INTERSECTING ADVANCES IN STEM CELL BIOLOGY AND STEM/TISSUE TRANSPLANT IMMUNOLOGY". Until then, the state of the art is still under trial and error experimentation. Thus, it is evident that at the time of the invention, the skilled artisan in the relevant art, while acknowledging the significant potential of stem cell therapy, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such therapeutic regimen. Although the instant specification provides a brief outline of a potential

therapeutic use of the bone marrow derived cells, it is not enabled for its full scope because the specification does not disclose any therapeutic regimen and effects either *in vivo* or *ex vivo*, in any subject for any neuron deficiency.

Claim 13 requires a step comprising mildly damaging nervous system of the transplant recipient. The specification teaches creating mild physical damage using a probe, needle or catheter to induce endogenous production of neuronal factors. However, the claimed mildly damage is not limited to a needle insertion, and embraces broader scale of brain damage. The effect of such mildly damage does not necessarily promoting the treatment goal. For example, *Sugaya et al* (CMLS 2003;60:1891-1902) teach, "IF AN INJECTION IS MADE INTO THE BRAIN, CONCOMITANT TISSUE DESTRUCTION WILL CAUSE MONOCYTE RECRUITMENT, AND ENSURING IMMUNE RESPONSE WILL ELIMIATE THE TRANSPLANTED CELLS" (1st paragraph, page 1893)

Claims further embrace allogenic and xenogenic transplantation, and it is well known in the art there are still major barriers for successful transplantation as of post-filing dates. *Game et al* (Wien Klin Wochenschr 2001;113:823-38) detailed different types of allogenic and xenogenic rejection (hyperacute, acute, chronic) and underlying mechanisms involving multiple pathways that lead to the failure of allogenic and xenogenic transplantation, and states, "WHILE MAJOR IMPROVEMENTS HAVE BEEN MADE IN THE PREVENTION AND TREATMENT OF HYPERACUTE AND ACUTE TRANSPLANT REJECTION, MOST GRAFTS WILL SUCCUMB TO CHRONIC REJECTION: THIS REFLECTS THE EXTENT OF OUR KNOWLEDGE OF THE MECHANISMS THAT DRIVE THESE PROCESSES", as for xenotransplantation, "NOVEL APPROACHES HAVE OVERCOME SOME EARLY ANTIBODY MEDIATED REJECTION EVENTS BUT THEN REVEAL A HUGE, INTENSE, ADAPTIVE CELLULAR RESPONSE". *Sugaya et al* (CMLS 2003;60:1891-1902) also

teach that the risk of immunological rejection limit the value of allogenic or xenogenic neuronal stem cell transplantation, "TISSUE REJECTION MAY NOT BE PARTICULARLY PROBLEMATIC IN NEURONREPLACEMENT STRATEGIES SINCE THE BRAIN DOES NOT PRODUCE A SIGNIFICANT LEVEL OF IMMUNE RESPONSE UNLESS TRAUMATIC DAMAGE HAS OCCURRED. NONETHELESS, IF THE BRAIN'S IMMUNE SYSTEM IS ACTIVATED ... UNDER DISEASE CONDITIONS, HETEROLOGOUS TRANSPLANTION MAY POSE SIGNIFICANT PROBLEMS" (2nd paragraph, right column, page 1893). It appears from the teaching of *Sugaya et al* the mildly damaging of the nervous system (claim 13) is fully capable of triggering such immune response.

Accordingly, in view of the state of the art at the time of instant filing date, in view of the quantity of experimentation necessary to achieve a therapeutic effect of the numerous neuronal deficiencies in an individual using bone marrow-derived cells, the lack of guidance provided by the specification as well as the absence of working examples with regard to therapy of neuron deficiency diseases, and the breadth of the claim directed to the use of neuronal stem cells in humans, it would required undue experimentation for one skilled in the art to make and/or use the claimed invention.

The following art rejections applied even though the Examiner is aware of the contradiction in the sections of enablement rejection and art rejection. In view of the Office policy of a compact prosecution, all issues relevant will put forward in the first action on merits.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-10, 13-21 are rejected under 35 U.S.C. 102(e) as being anticipated by *Sanchez-Ramos et al* (US 2002/0146821).

Sanchez-Ramos et al teach a method for treating a neuronal deficiency comprising administering bone marrow-derived cells to an individual having a neurodegenerative disorder such as Parkinson's disease (implicating such use in a human subject, paragraph 0039), wherein the cells are autologous, allogenic or xenogenic (paragraph 0033), wherein the cells are genetically modified to carry a marker cell for tracing (paragraph 0050), or carrying a gene of therapeutic interest (paragraph 0112), wherein the cells are treated with a neuronal factor such as NGF to promote neuronal differentiation, and the factors would then be administered into the subject along with the cells (paragraph 0035), wherein the cells are administered by intravenous administration (parenteral route), or intrathecal, intraventricular administration, (meeting claim limitation of direct administration into a site of the subject's central nervous system, paragraph 0074). Intrathecal administration uses a needle directly to the brain tissue causing mildly damaging to the nervous system, thus meets the limitation of claim 13. *Sanchez-Ramos et al* teach that systemic or striatum

infusion is a means of delivering bone marrow-derived cells (paragraph 0050).

Therefore, *Sanchez-Ramos et al* anticipate instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 8, 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Sanchez-Ramos et al* (US 2002/0146821), in view of *Weiss et al* (6,071,889).

The teaching of *Sanchez-Ramos et al* has been discussed in detail above. Especially, they teach the need of using NGF for differentiating bone marrow-cells toward the neuronal lineage. *Sanchez-Ramos et al* do not teach administering NGF separately from the bone marrow-derived cells intrathecally.

However, before the effective filing date of instant application, *Weiss et al* teach administering neuronal growth factors along with the neuronal stem cells *in vivo* to promote the *in vivo* proliferation and differentiation of neural stem cells and the

treatment of neurodegenerative diseases (abstract and the Section bridging columns 10 & 11), wherein the neuronal growth factors include NGF (column 5, lines 15 to 25), wherein the factors could be administered together or separate with cells (column 11, lines 2-35), wherein the injection is at the site of neurodegeneration (column 6, lines20-21).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Sanchez-Ramos et al,* with that of *Weiss et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the methods to arrive at the claimed invention because bone marrow-derived cells are relatively easy to obtain as neuronal cell progeny, particularly if the patient's has a diseased brain, and administering the combination of bone marrow-derived cells and neuronal growth factors would enhance the proliferation and differentiation of the stem cells thus enhancing the treatment effects. Thus, the claimed invention as a whole was clearly *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942 (571-272-0730, after the Office relocation in January, 2004). The examiner can normally be reached on 9:30 am - 6 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JANICE LI
PATENT EXAMINER

Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
November 28, 2003